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Anticipation of aversive stimuli activates extended amygdala in unipolar depression ☆

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Abstract

According to cognitive theories, negative cognitions including negative attitudes towards the future are key factors associated with depressive disorder. We investigated the neural correlates of anticipation of emotional stimuli in patients with unipolar depression to reveal influences of future thinking on brain activity. We used functional magnetic resonance imaging (fMRI) to study 12 female patients with stable antidepressant medication and 12 healthy women. Subjects were presented with positive, negative and neutral pictures that were announced by a congruent cue. Subjects were instructed to expect and subsequently watch the pictures. After scanning, subjects filled the Emotion Regulation Questionnaire (ERQ) to assess the regulation strategies suppression and reappraisal. Compared to the healthy control group, during expectation of negative vs. neutral or positive stimuli the patients showed significantly more activation within the sublenticular extended dorsal amygdala (SLEA) bilaterally but did not differ from controls upon expecting positive stimuli. Hamilton depression scores of the patients correlated positively with activation of the left and right ventral amygdala during expectation of negative stimuli. Furthermore, we found a negative correlation of ventral amygdala activation in the patients with reappraisal scores comprising the ability to limit emotional responding by re-interpreting emotion-eliciting situations. We interpret enhanced activation in the amygdala/SLEA as a possible consequence of altered future thinking in patients suffering from depression. Supporting cognitive theories, this finding does represent evidence that altered cognitions as potentially involved in expectation result in differences in brain activity.

Keywords: Depression; fMRI; Future thinking; Cognitive theory of depression; Anticipation of emotional stimuli

1. Introduction

Negative attitudes towards future events, together with feelings of hopelessness in general, are important symptoms of depressive disorders. Patients often are not able to look forward to upcoming positive events and take potentially negative prospects more grave than healthy subjects. According to cognitive theories of mood disorders (Beck et al., 1979), a systematic bias in processing of information from the environment has been proposed as a psychological explanation for these phenomena.

Recently, functional neuroimaging has made important contributions towards a better understanding of the pathophysiology of depression. Metabolic activity of the amygdala could be predicted by scores of negative affect and depression (Abercrombie et al., 1998; Drevets et al., 1992) and activity in the anterior cingulate cortex was

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related to response to antidepressant treatment (Buchsbaum et al., 1997; Davidson et al., 2003; Mayberg et al., 1997, 2000). Furthermore, functional imaging studies revealed task-related differences between patients and healthy controls: Activation of the amygdala in acute depression was increased in response to sad faces (Fu et al., 2004; Surguladze et al., 2005) negative pictures (Davidson et al., 2003) and words (Siegle et al., 2002). Besides amygdala, prefrontal and cingulate cortex, basal ganglia and secondary visual areas showed altered responses to emotional stimuli in depression (Davidson et al., 2003; Fu et al., 2004; Surguladze et al., 2005).

Up to now, imaging studies of depression have mainly investigated altered *perception* of emotional stimuli. But from a psychological point of view alterations in *attitudes* towards stimuli or events may play an even greater role in the pathophysiology of depression. According to cognitive theories (Beck et al., 1979; Teasdale et al., 1998) cognitions actually may be the cause for altered perception of environmental stimuli, and cognitive styles have been found to predict vulnerability to depression (Alloy et al., 1999). Biased future thinking in depression has been suggested to rely on an easier access to negative (but not positive) memories or cognitions and on altered simulation processes of future events resulting for example in an overestimation of the probability of negative future events (MacLeod and Rutherford, 1999). The way how dysphoric patients think about a certain event, how they attribute it, was found to influence the perception of the likelihood of similar experiences in the future (Cropley and MacLeod, 2003). This supports the notion that expectations towards a certain event seem to be biased by cognitions or attitudes towards such events and by past experiences with it. We suggest from this, that the investigation of the anticipation of emotional stimuli has the potential to reveal influences of attitudes biasing expectation processes in depression as well. Furthermore, in healthy subjects, expectation of negative stimuli like fear, pain or aversive pictures has been shown to activate brain regions involved in depression – like the amygdala, prefrontal, insular, and cingulate cortex (Nitschke et al., 2006; Ploghaus et al., 1999; Porro et al., 2003; Ueda et al., 2003).

It has been suggested that the information processing bias in affective disorders arises from a dysfunctional interaction of bottom-up emotional activation and top-down attentional control (Mathews and MacLeod, 2005). The assessment of emotion regulation strategies can be a means to further characterize the control processes involved. Gross and John (2003) proposed two major forms of emotion regulation strategies: reappraisal and suppression. Cognitive reappraisal is defined as a form of cognitive change that involves construing a potentially emotion-eliciting situation in a way that changes its emotional impact (Lazarus and Alfert, 1964) while suppression is defined as a form of response modulation that involves inhibiting of ongoing emotion-expressive behavior. Reappraisal is considered an antecedent strategy apt to successfully reduce the behavioral and experiential component of negative future emotions. In contrast, suppression is considered a response-focused strategy primarily modifying the behavioral aspect of negative emotional responses but not their experience. It has been suggested that suppression is related to negative cognitions and depressive thinking while reappraisal has a rather protective effect (Gross and John, 2003) concerning mood disturbances.

We investigated the neural correlates of the anticipation of visual emotional stimuli with positive or negative affective valence. Anticipating negative events may easily elicit anxiety and comorbid anxiety is frequently seen in depression. Amygdala and insula are not only relevant in depression, but were found activated as well in anxiety disorders, e.g. when socially phobic patients anticipated making public speeches (Lorberbaum et al., 2004).

To put an emphasis on depression in comparison to classical anxiety disorder we used clearly negatively valenced pictures from the IAPS of disgusting but assumably not fear-inducing content. Previous studies on the anticipation of aversive events including our own found involvement of insula (Simmons et al., 2004), prefrontal and cingulate cortex (Herwig et al., in press) and amygdala. Hereby, rather the dorsal part of the amygdala within the region of the sublenticular extended amygdala seemed to be involved (Nitschke et al., 2006).

Using functional magnetic resonance imaging (fMRI) we tested two hypotheses concerning cognitions and future thinking in depression:

First hypothesis: Expectation of future emotional stimuli is biased in depression. Based on Beck's theory and the notion that attitudes have an influence on emotional reactions, we expected to find altered brain activity in subjects suffering from depression compared to healthy subjects, especially in regions previously identified to be involved in the processing of aversive stimuli.

Second hypothesis: Preferential emotion regulation strategies of subjects with a diagnosis of depression will differ from those in healthy subjects and may help to explain altered brain activities.

2. Methods

2.1. Subjects

13 female patients with a diagnosis of a moderate or severe depressive episode or recurrent depressive disorder according to the International Classification of Diseases (ICD-10: F32.1, F32.2, F33.1 or F33.2) and 12 healthy female control subjects were primarily included in the study (Table 1). Diagnoses were assessed with a psychiatric interview by a specialist psychiatrist involved in the patient's treatment after admission of the patient and confirmed before enrollment. Interviews comprised a general part concerning the patient's history and a structured part to confirm the diagnosis according to ICD-10 criteria. All

Table 1
Demographic and clinical characteristics of the sample

	Depressed patients ($n = 12$)	Healthy subjects ($n = 12$)
Age	23–51 (mean: 41.2 y)	23–54 (mean: 40.7 y)
Education	3 qualified for university	4 qualified for university
Number of episodes	1 (3 patients) to 5	–
Exclusion criteria	• Any psychotic symptoms • Suicidal ideation • Medication with neuroleptics • Sedative medication other than Zopiclone 7.5 mg/night or up to 1 mg Lorazepam/day • Comorbid axis I disorder currently or in the past, including bipolar I or II disorder, anxiety disorder and substance abuse	• Any history of psychiatric or neurological disorder • Psychotropic medication of any kind
Antidepressant medication (patients only)	*6 patients*: SSRIs only *2 patients*: SSRI + reboxetine *2 patients*: SSRI + mirtazapine *1 patient*: SNRI only *1 patient*: SSRI + trimipramine	

patients were in-patients of the Department of Psychiatry at the University Hospital of Ulm, Germany, or patients of the day clinic with an acute episode of depressive disorder of the unipolar subtype upon admission and stable antidepressant medication for at least two weeks. One patient was subsequently excluded because she suffered from her first hypomanic episode shortly after participating in the study. Patients were recruited in a sub- or postacute state of depression between 2 and 6 weeks (12 weeks in one subject) after their initial admission to the hospital. All participants, patients and controls, gave written informed consent after complete description of the study. The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the ethics committee of the University of Ulm, Germany. We primarily investigated women only, as several previous studies suggested sex differences in response to negative visual stimuli (Cahill et al., 2001, 2002).

2.2. Ratings and psychological testing

Scores on German versions of the Hamilton Depression Scale (HAMD, 21 items, minimal score: 0, maximal score: 63 (CIPS, 2005); and the Montgomery Asberg Depression Scale (MADRS, 10 items, minimal score: 0, maximal score: 60 (CIPS, 2005); of the patients were assessed within 24 h before or after scanning by an experienced psychiatrist otherwise not involved in the study or the treatment of the patient. Before scanning, patients and healthy subjects were asked to fill three questionnaires: the State-Trait Anxiety Inventory for Adults (STAI, German Version) with ratings for state (STAIS, 20 items, minimal score: 20, maximal score: 80) and trait (STAIT, 20 items, minimal score: 20, maximal score: 80) anxiety (Laux et al., 1981), the Beck Depression Inventory BDI (German Version, 21 items, minimal score: 0, maximal score: 63 (Hautzinger et al., 1995)); and a German version (in-house translation) of the Emotion Regulation Questionnaire (ERQ) with two scores, one for 'reappraisal' and one for 'suppression' representing the two different emotion regulation strategies as proposed by Gross and John (2003). The instruction and wording of the German version of the questionnaire was held as close as possible to the original English version. The number of questions, minimal and maximal scores and structure of the questionnaire remained unchanged. The questionnaire comprises 10 items (statements), 6 to assess the reappraisal score (average score of the 6 items, maximum 7), 4 for the average suppression score (average score of the 4 items, maximum 7). Subjects are asked to rate on a scale from 1 (strongly disagree) to 7 (strongly agree) how they agree with each of the 10 statements concerning the management of emotions.

2.3. Task and stimuli

While being scanned, subjects were presented with 45 pictures selected from the international affective picture system (IAPS) with pleasant, disgusting or neutral content. Fifteen pictures of each valence appeared in a randomized order. Each stimulus was announced by a matching cue, depicting either a smiling, a non-smiling or a neutral 'smiley'-symbol. Cues were presented for 1000 ms followed by an expectation period of 6920 ms. After that, pictures were presented for 7920 ms (4 TRs), followed by an intertrial-interval of 15,840 ms (8 TRs) to allow the BOLD signal to level off. Subjects were instructed to expect a positive, negative or neutral picture corresponding to the cue and to attentively perceive the following picture and its emotional content. We used negative pictures only of disgusting valence as those are not primarily supposed to induce fear. They were rated clearly negative in a pilot behavioral study in 25 subjects and were thus suited to induce a strong negative emotional stimulation.

2.4. fMRI Acquisition

T2*-weighted functional images and T1 anatomical volumes were acquired using a 1.5 T Siemens Symphony

scanner (Erlangen, Germany) equipped with a head coil. Seven hundred and thirty-two volumes of functional images were obtained using an echo-planar pulse sequence (EPI). Each volume comprised 22 axial slices covering the whole cerebrum (TR/TE = 1980/40 ms, 64×64 matrix). Slice thickness was 4 mm with 1 mm gap resulting in a voxel size of $3 \times 3 \times 5$ mm. Stimuli were presented with LCD video goggles (Resonance Technologies, Northridge, CA). For each subject, three-dimensional T1 weighted anatomical volumes ($1 \times 1 \times 1$ mm voxels) were acquired.

2.5. fMRI data analysis

Image processing and statistical analysis were carried out using Statistical Parametric Mapping (SPM2, Wellcome Department, London, UK). Preprocessing of the functional scans included slice timing, realignment to correct for motion artifacts using the first scan as a reference and spatial normalisation to a standard template (Montreal Neurological Institute, MNI) with a resampled voxel size of $3 \times 3 \times 3$ mm. Smoothing was applied with an 8 mm Gaussian kernel. Intrinsic autocorrelations were accounted for by AR(1) and low frequency drifts were removed via high pass filter.

After preprocessing, first level analysis was performed on each subject estimating the variance of voxels according to a general linear model. The three expectation periods including presentation of the cue (positive, negative, neutral expectation) and the three different picture presentation periods (positive, negative, neutral presentation) were each modeled separately as a boxcar function and convolved with the hemodynamic response function. This resulted in six regressors of interest. Realignment parameters were included in the model.

The contrast images of parameter estimates were then included in a second level group analysis (random effects model), treating intersubject variability as a random effect to account for interindividual variance. Two-sample *t*-tests were used to investigate between group effects. Statistical maps were thresholded at $p < 0.001$ uncorrected for multiple comparisons. Results were extent threshold corrected at 0.05 at the cluster level. Small volume corrections (Worsley et al., 1996) were applied for amygdala/extended amygdala at $p < 0.05$ as we had a priori hypotheses about these regions.

Distinctions between dorsal/sublenticular extended and ventral amygdala were made as suggested by Kim et al. (2004) and in line with the boundaries defined in the Mai et al. atlas (Mai et al., 1997). Accordingly, only clusters fully located superior to a line of $z = -12$ in MNI space (Talairach: $z = -10$ [for $y = \pm 7$]; http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) where classified as part of the dorsal amygdala or SLEA, clusters fully located inferior to this line were classified as part of the ventral amygdala.

For the analysis of the signal time course data, functional regions of interest (ROIs) of the differential SLEA activations were defined. For each subject, the mean-corrected 1st eigenvariate time series of all voxels within a predefined region was extracted. Data were then averaged event-related, separately for negative, positive and neutral events Paired *t*-tests were used to assess differences in brain activation at the time of each scan between conditions (negative/neutral) represented by the respective 1st eigenvariate values.

The anatomical ROIs provided by the SPM toolbox 'WFU_PickAtlas' (Maldjian et al., 2003) were used to investigate time courses within the ventral Amygdala. The respective ROIs from the PickAtlas comprise the ventral amygdala only and did not contain voxels superior to MNI $z = -12$.

Regression analyses at the second level were computed to explore whether individual differences in the first level contrast images co varied with individual differences as assessed in the rating scales and questionnaires with one regressor modeling the mean of brain activation and the other the mean-corrected test score.

Statistical analysis of the rating data and scores was performed using STATISTICA 6.0 computing Mann–Whitney *U*-tests to reveal differences between groups and Spearman's correlation coefficients to analyze relations between variables within the patient group.

2.6. Validation: Comparison with pilot results

To check the validity of our paradigm, we calculated additional contrasts separately in the patients and in the controls group. One-sample *t*-tests were used to investigate within group effects. Statistical maps were thresholded at $p < 0.001$ uncorrected for multiple comparisons. In line with other studies of the anticipation of aversive stimuli (Nitschke et al., 2006), the main findings of our previous pilot study (Herwig et al., in press) were activation of insula, prefrontal areas, thalamus and specifically the anterior cingulate cortex (ACC) upon expectation of negative stimuli. We expected to replicate these regions calculating contrasts as in the pilot study comparing expectation of negative stimuli with presentation of negative stimuli (exp.neg. > pres.neg.) and expectation of negative stimuli with expectation of neutral stimuli (exp.neg. > exp.neut.).

3. Results

3.1. Subject data and questionnaires

Patients were recruited in a sub- or postacute state of unipolar depression (Table 2). Three patients were almost upon remission as measured with HAMD (scores <13) but with still manifest symptoms according to MADRS and BDI. One patient was included in a state of recovery after 2 weeks of stable treatment. Exclusion of this patient from the analyses did not substantially alter results as reported here.

Anxiety scores (Table 2) in our patients' group were higher than in healthy control subjects in general according

Table 2
Subject data and questionnaires: median scores, 25% and 75% quartiles

	Depressed patients ($n = 12$) 50%, [25%, 75%] quartiles	Healthy subjects ($n = 12$) 50%, [25%, 75%] quartiles
HAMD	18.5 [11.5, 22.25]	–
MADRAS	23 [18.5, 31]	–
BDI	19.5 [16.25, 33.5]	2 [1, 4][c]
STAI		
STAI-T	61 [53, 67]	33 [28, 35.5][c]
STAI-S	58 [52, 59]	29 [28, 29.5][c]
ERQ		
Reappraisal	3.7 [3.0, 4.7][b]	4.3 [3.3, 4.8]
Suppression	4.1 [2.9, 5.9][a]	2.5 [2.2, 2.8]

HAMD: Hamilton Depression Scale; MADRAS: Montgomery Asberg Depression Scale; BDI: Beck Depression Inventory; STAIT/STAIS: State-Trait Anxiety Inventory for adults; ERQ: Emotion Regulation Questionnaire (Gross and John, 2003); minimal value: 1; maximal value: 7; SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Selective Noradrenaline Reuptake Inhibitor.

[a] Patients score significantly higher than healthy subjects (Mann–Whitney U-test, two-tailed: $Z = 2.9$; df = 22; $p < 0.004$).

[b] No significant difference between patients and healthy subjects (Mann–Whitney U-test, two-tailed: $Z = -0.72$; df = 22; $p < 0.47$).

[c] From five of the control subjects we did not obtain BDI and STAI scores but only the ERQ.

to the German validation in a large sample of women but comparable to the scores of a sample of depressed subjects reported in the test manual (Laux et al., 1981). Control subjects marked average to low levels of anxiety.

Analyses of the ERQ revealed significantly higher ratings for the 'suppression' items in the patients compared to control subjects (Table 2) whereas the ratings for the 'reappraisal' items were higher in the control group but without reaching significance.

Spearman's correlation coefficients were computed to reveal interrelationships between questionnaire and rating scores and thresholded at $p < 0.05$ (10 degrees of freedom). As expected, BDI scores were highly correlated with HAMD ($r = 0.71$), MADRAS ($r = 0.90$) and STAI-S ($r = 0.70$). STAI-T scores correlated positively with ERQ scores for 'suppression' ($r = 0.59$). Reappraisal' ratings were negatively correlated with both HAMD ($r = -0.71$) and MADRAS ($r = -0.60$) scores.

All subjects, patients and controls, confirmed after scanning that they anticipated a congruent picture after the cues and subsequently watched the pictures as instructed.

3.2. FMRI analysis – between group effects

Two-sample t-tests between groups comparing contrasts of interest in patients and controls revealed significantly elevated activations only in the patients compared to the control subjects (Table 3). No activation was found significantly stronger in controls than in patients in any contrast of interest.

Activation within the sublenticular extended amygdala (SLEA) was found for expectation of negative vs. neutral stimuli (Fig. 1) and as well for expectation of negative vs. positive stimuli when comparing patients to controls. Expectation of negative vs. expectation of positive stimuli furthermore led to significantly higher activation of the lateral and medial frontal cortex in the patients than in the controls. In addition, we found the dorsal anterior cingulate cortex (ACC) being significantly more active in the patients compared to controls upon presentation of negative vs. neutral stimuli (Fig. 2) and the subgenual ACC upon presentation of positive vs. negative stimuli.

To ensure that the results of our group-by-condition interaction contrasts were clearly driven by actually elevated fMRI signal in the patients group, we computed the respective contrasts in the patients group only and used them as masks. All reported clusters were still present after

Table 3
Group maximum t-values and MNI coordinates of activation foci for the two-sample t-test analyses (22 degrees of freedom) between contrasts of interest

Contrast of interest/cerebral region	BA	R/L	Voxels	Z-score	Coordinates of peak activity		
					x	y	z
Expectation negative vs. neutral stimuli							
Amygdala/SLEA	–	L	16	3.78	−21	0	−9
Amygdala/SLEA	–	R	43	4.24	27	−3	−9
Expectation negative vs. positive stimuli							
Gyrus frontalis medialis (posterior)	6	M	83	4.15	−3	−6	69
Dorsolateral prefrontal cortex	9	L	15	3.85	−51	21	33
Amygdala/SLEA	–	R	11	3.83	24	−3	−6
Presentation negative vs. neutral stimuli							
Dorsal anterior cingulate gyrus	32	R	17	4.05	12	21	33
Presentation positive vs. neutral stimuli							
Subgenual gyrus	25	M	17	3.38	−3	24	−15

All comparisons show elevated activation in the patients compared to control subjects in several conditions, i.e. represent group-by-condition interactions. Statistical maps were thresholded at $p < 0.001$ uncorrected for multiple comparisons. Results were extent threshold corrected at 0.05 at the cluster level. Small volume corrections (Worsley et al., 1996) were applied for amygdala/SLEA. All reported clusters were still present after masking the results of the two-group comparison with the respective contrast in the patients group only. Masks were thresholded at 0.005 at the voxel- and 0.05 at the cluster-level. Resampled voxel-size: $3 \times 3 \times 3$ mm.

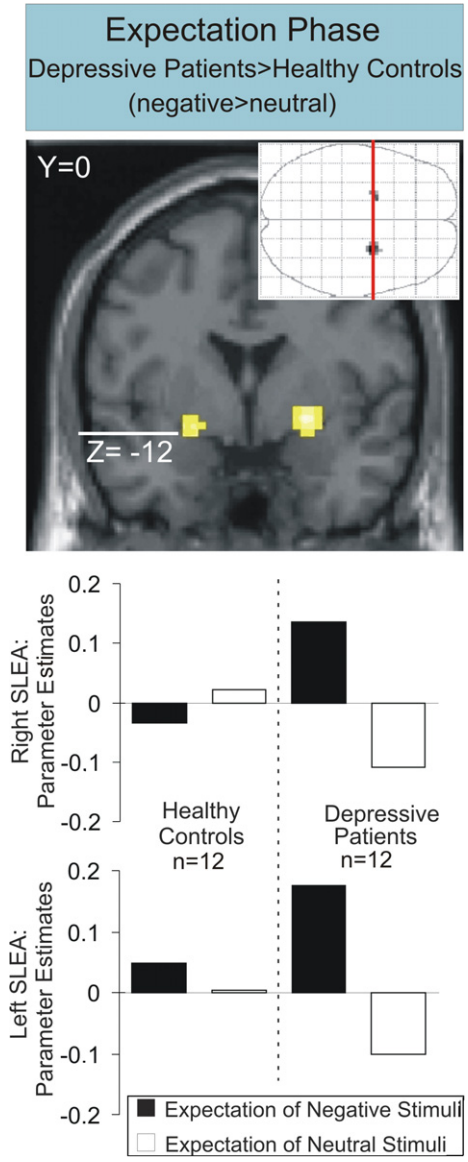

Fig. 1. Increased activity in patients suffering from depression compared to healthy controls as found in left and right sublenticular extended amygdala (SLEA) for expectation of negative vs. neutral stimuli (whole-brain analyses). The plots show the mean parameter estimates of the respective regressors (expectation of negative/neutral stimuli) at the peak voxels (local maxima of the contrast negative vs. neutral stimuli) within right (27/−3/−9) and left (−21/0/−9) dorsal amygdala/SLEA. Maps were thresholded at $p < 0.001$ uncorrected for multiple comparisons. Results were extent threshold corrected at 0.05 at the cluster level. Small volume corrections (Worsley et al., 1996) were applied for amygdala/SLEA.

masking the results of the two-group comparison with the respective contrast in the patients group only.

No significant differences or trends between groups were found for expectation of positive vs. neutral stimuli. ROI time course data (Fig. 3, right) confirmed that differential activation (negative > neutral) within the SLEA in the patients occurred predominantly during the expectation, not the presentation period. In the controls, some differential activation in the SLEA was found upon expectation and presentation as well. Effects (negative > neutral) in the controls were markedly smaller compared to the patients. Time courses from anatomical ventral amygdala ROIs (Fig. 3, left) of the patients and controls furthermore suggest that the differential effects during expectation of negative stimuli were less prominent than within dorsal amygdala (SLEA) regions. Effects of picture presentation (negative > neutral), especially in the controls, were more prominent in the ventral amygdala.

In order to test whether the presentation of the cues (smileys) on their own might exert a significant BOLD effect, we separately scanned six healthy subjects while presenting the cues only and analyzed the individual hemodynamic response related to the cue presentation. In these subjects, there were no consistent valence related effects in regions known to be associated with emotion processing in each individual analysis on a significance level of $p < 0.05$ uncorrected.

Furthermore, we analyzed the differential effects (negative > neutral) during expectation in the patients in more detail: for depressed patients, a negative smiley might be more salient than for healthy controls and thus might account for the differential effects. Therefore, the presentation of the negative cue for 1 s at the beginning of the anticipation period alone could possibly explain our findings. If so, however, the activation related to the first half of the 4 scan (~8 s) anticipation period – when the cue was actually presented – should be higher than activation related to the second half. To test this hypothesis, we set up a new SPM model with 2 instead of one regressor for each negative and neutral expectation: '1st half negative expectation', '2nd half negative expectation', '1st half neutral expectation', '2nd half neutral expectation' (4 s each) instead of 'negative expectation' and 'neutral expectation' (8 s each). Paired t-tests between individual parameter estimates of effects for the contrast (negative > neutral expectation) in the SLEA comparing effects during first and second half of the anticipation period did not support this interpretation (left SLEA: $t(11) = 0.18/p = 0.86$; right SLEA: $t(11) = -0.43/p = 0.67$).

3.3. fMRI-analyses: correlations with test scores

Brain activation (individual values of modeled effects) related to test scores was identified within the regions showing differential activation when comparing patients to controls: Amygdala/SLEA, prefrontal cortex, dorsal and subgenual ACC.

We found a positive correlation of activity within bilateral ventral amygdala and individual HAMD scores in the patients upon expectation of negative stimuli (Table 4, Fig. 4). Corresponding to the fact that reappraisal scores and HAMD scores were negatively correlated, we observed bilateral ventral amygdala activation being negatively correlated with reappraisal scores at a marginal significance level of $p < 0.006$ uncorrected for multiple comparisons (Table 4, Fig. 5). We did not find similar activity in the group of healthy subjects down to a threshold of $p < 0.01$.

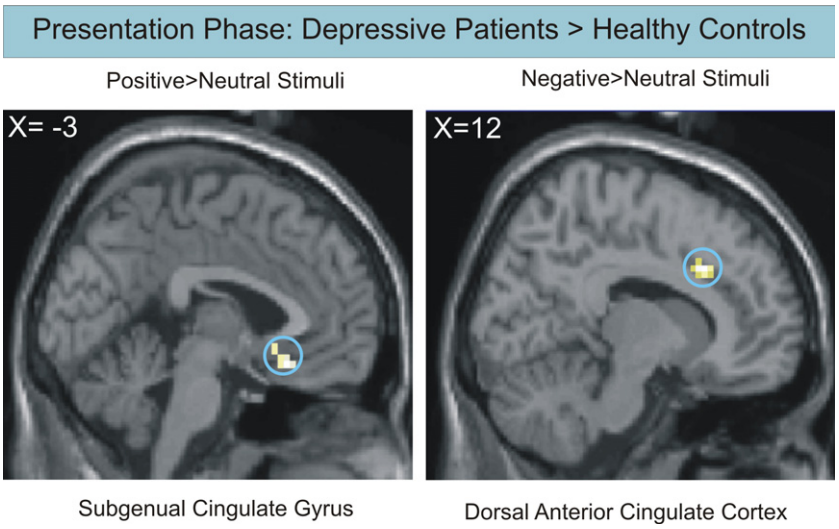

Fig. 2. Increased activity in patients with unipolar depression compared to healthy control subjects for presentation of negative vs. neutral and positive vs. neutral affective stimuli (whole-brain analyses). Maps were thresholded at $p < 0.001$ uncorrected for multiple comparisons. Results were extent threshold corrected at 0.05 at the cluster level. Small volume corrections (Worsley et al., 1996) were applied for amygdala/SLEA.

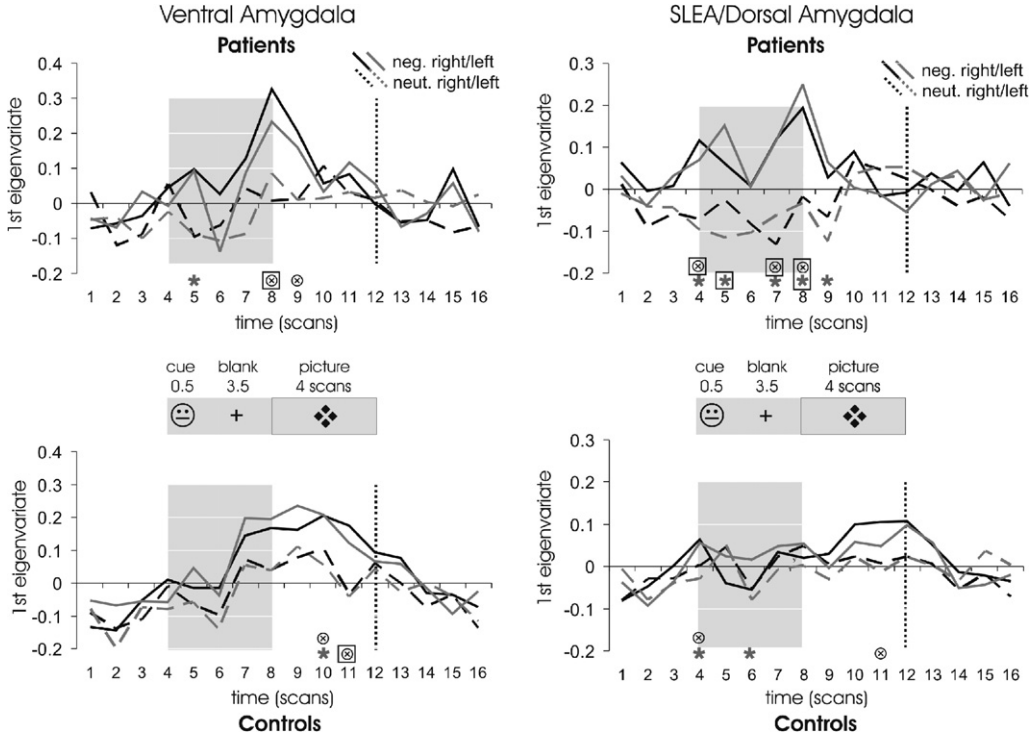

Fig. 3. (right) 1st eigenvariate time courses within left and right functional sublenticular extended amygdala (SLEA) ROIs as found for the contrast expectation of negative stimuli > expectation of neutral emotional stimuli. (left) 1st eigenvariate time courses within left and right ventral amygdala (anatomical ROIs). Time courses for expectation and presentation of negative (straight lines) and neutral (dashed lines) events are presented. A lag of 6 s of the hemodynamic response was assumed when depicting the task relative to the time courses. Expectation phases (cue and blank) and picture presentation had a duration of 4 scans (7920 ms) each. Cues were presented for 1 s or 0.505 scans at the beginning of the expectation period. ⊗/★: significant differences (paired t-tests, $p < 0.05$) between 1st eigenvariate values per scan for negative and neutral events for right (⊗) and left (★) amygdala. Signs in boxes (□): $p < 0.005$.

3.4. Validation: comparison with pilot results

In the control subjects we replicated the finding from our pilot study (Herwig et al., in press) of ACC activation, particularly the anterior part, upon expectation of negative stimuli. Both contrasts, [1] exp.neg. > exp.neut. and [2] exp.neg. > pres.neg. revealed involvement of this structure ([1]$x/y/z$: 0/18/30, $Z = 3.72$, 56 voxels and [2]$x/y/z$: −9/

36/18, $Z = 4.29$, 39 voxels). Additionally, we replicated the finding of posterior cingulate involvement in the contrast exp.neg. > pres.neg.

In the patients we found activation within the anterior cingulate upon exp.neg > exp.neut ($x/y/z$: −9/15/42, $Z = 3.64$, 26 voxels) but not upon exp.neg. > pres.neg.

4. Discussion

According to our hypotheses, the main findings of our study are (1) a significant difference in brain activation, especially in the dorsal amygdala/SLEA, upon anticipation of negative stimuli between patients with unipolar depression and healthy controls, (2) a positive correlation between ventral amygdala activation and severity of depression as measured by HAMD and (3) significant differences in preferential emotion regulation strategies between the two groups at the behavioral level and a negative correlation between reappraisal scores with ventral amygdala activation at the neural level in the patient group. Findings from our pilot study of a specific involvement of the anterior cingulate cortex upon expectation of negative stimuli were confirmed.

4.1. Anticipation of emotional stimuli in depressed patients

We assume that our data support the notion that anticipation of future events is altered in patients suffering from unipolar depression. We could demonstrate that particularly the dorsal amygdala/SLEA is more active in patients than in control subjects upon anticipation of negative emotional stimuli compared to neutral as well as to positive stimuli. Expectation of emotional stimuli comprises cognitive processes like identification and evaluation of context and emotion and we therefore suggest that it may reflect underlying cognitions and attitudes towards future events. We present evidence that anticipation, possibly involving altered cognitions, and not only mere perception of emotional stimuli leads to functional changes in limbic brain areas relevant for emotional processing in depression.

As we used symbols with some emotional content (smileys) as cues, an alternative explanation of our findings could be a simple effect of depressed patients perceiving emotional stimuli differently than controls. However, the cues were only shown for about 1/8th of the whole expectation period and presented on their own did not elicit valence related effects in a separate experiment to validate our results. But while our paradigm may be an effective anticipation paradigm in healthy subjects, the sad face symbols used as cues may carry specific salience for the depressed patients not relevant to the controls. The specific salience of sad stimuli to depressed patients has been demonstrated before (Fu et al., 2004) and could explain our findings. However, our additional analysis modeling first and second half of the expectation period gave no evidence for this explanation as the amygdala activation was not higher during the first compared to the second half of expectation period. Furthermore, we did not find differences between patients and controls during presentation of actual emotional pictures shown for a much longer time and clearly known to elicit emotional responses. These findings point to a true expectation effect independent of the inherent emotional valence of the visual cues. This could add neurobiological evidence to cognitive theories suggesting that a negative bias in thinking influences emotionality. Likewise, our data add evidence to the hypothesis of a hyperactivation of the amygdala in depressed patients as previously demonstrated in resting state (Drevets, 2000) and activation studies (Yurgelun-Todd et al., 2000), review in Whalen et al. (2002).

Alternatively, our findings can be interpreted as a conditioning effect, i.e. as a shift of the picture effects to the unconditioned stimulus announcing the pictures as proposed for ventral striatal activity due to rewarding stimuli (Knutson et al., 2001). Simple conditioning effects of the amygdale seem to fade with time. Studies of conditioning in animals (rats) (Quirk et al., 1997) as well as imaging studies of human subjects in the context of emotional stimuli (Breiter et al., 1996; Buchel and Dolan, 2000) have shown rapid habituation of the activity in the amygdala upon repeated (4 or 5 trials) presentation of the same aversive conditioned stimuli. Interpreting our results as a consequence of altered conditioning in the patients would point to altered habituation processes of amygdala activation in depression. From a perspective of implicit learning one could argue that habituation could occur faster in the controls, resulting in the relatively increased activity in the patients. To investigate this possibility we calculated the parameter estimates of modeled effects for each early, middle and late expectation phases (first five, middle five and last five trials per condition) separately. The differential effect during expectation (negative pictures compared to neutral pictures) was consistently higher in the patients than in the controls throughout all three phases. This finding was clearly driven by constantly high activation upon expectation of negative stimuli in the patients. Controls did not show decreases of activation over time but constantly low differential effects in all three phases. Therefore, the habituation interpretation seems less likely.

Enhanced involvement of prefrontal areas upon expectation of negative compared to positive stimuli as found in our study supports the notion of altered cognitive control processes in subjects suffering from depressive disorder compared to healthy controls. Increased activation of prefrontal areas has been associated with regulatory processes decreasing amygdala activation in healthy subjects (review in: Ochsner and Gross, 2005). In this light, the prefrontal hyperactivation in the depressed subjects relative to controls as found in our study can be interpreted as physiological inefficiency parallel to interpretations of functional prefrontal hyperactivation in schizophrenia (Callicott et al., 2003). Dysfunction of prefrontal control in major depression may lead to increased task-related prefrontal

Table 4
Activation peaks within previously hypothesized regions correlating with test scores (Hamilton Depression Scale, HAMD; Emotion Regulation Questionnaire, ERQ, Regulation)

Expectation of negative stimuli (depressive patients)	R/L	Voxels	*Z*-score	Coordinates of peak activity		
				x	*y*	*z*
HAMD: positive correlation						
Amygdala (ventral part)	R	20	4.14	24	3	−21
Amygdala (ventral part)	L	15	3.87	−21	−6	−21
ERQ/reappraisal: negative correlation						
Amygdala (ventral part)	R	2	2.53[a]	24	3	−21
Amygdala (ventral part)	L	15	2.58[a]	−18	−3	−21

Maps were thresholded at $p > 0.001$ (10 degrees of freedom) uncorrected for multiple comparisons. Results were extent threshold corrected at 0.05 at the cluster level. Small volume corrections (Worsley et al., 1996) were applied for amygdala/SLEA. Correlations were computed with the first level contrast images for the regressor 'expectation of negative stimuli'. Resampled voxel-size: $3 \times 3 \times 3$ mm.

[a] $p < 0.006$ uncorrected for multiple comparisons.

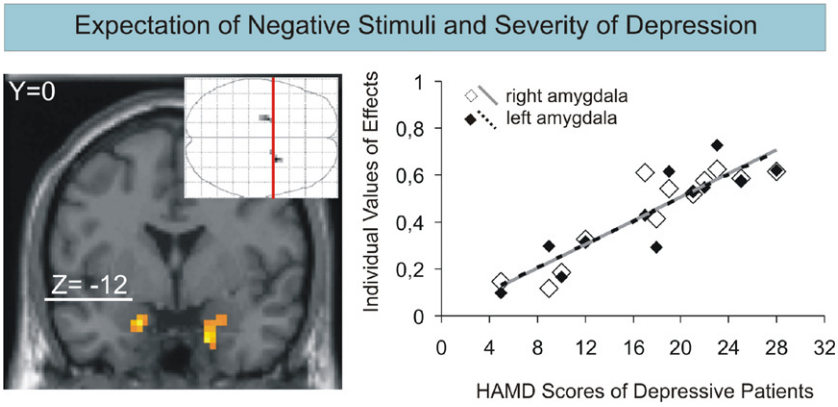

Fig. 4. *Expectation of negative stimuli:* Individual values of modeled effects over the whole brain correlating with scores on Hamilton Depression Scale (HAMD). Correlations were computed with the first level contrast images for the regressor 'Expectation of Negative Stimuli'. *Plot:* Correlation curves of values of modeled effects at local maxima within left ($r = 0.89$) and right ($r = 0.91$) amygdala and test scores. Maps were thresholded at $p < 0.001$ uncorrected for multiple comparisons (colored picture: $p < 0.005$ for demonstration purposes). Results were extent threshold corrected at 0.05 at the cluster level. Small volume corrections (Worsley et al., 1996) were applied for amygdala/SLEA.

activation relative to controls representing inefficient down-regulation of amygdala activation.

4.2. The functional role of the SLEA

The SLEA is a region with multiple connections to other limbic brain regions, including the lateral basal cortical amygdala. It is supposed to represent a region capable of coordinating activities in different areas of the limbic lobe forebrain relevant for understanding pathophysiology and treatment of neuropsychiatric disorders (Heimer et al., 1997). Neurons in the extended amygdala containing corticotrophin-releasing factor which is relevant for physiological responses to stress underline the role of this area in major depression and anxiety disorders (Heimer, 2003).

Several previous imaging studies have demonstrated an involvement of the SLEA in emotional processing. Positive as well as negative facial expressions (Whalen et al., 1998), aversive (Phan et al., 2003) but also positive visual stimuli (Liberzon et al., 2003) elicited activity in this limbic area. Although the spatial resolution of fMRI does not allow to precisely locate the SLEA, we interpreted our findings within the ventral basal forebrain as SLEA as our coordinates were consistent with those from previous imaging studies. Importantly, activation of the SLEA has been found to modulate cognitive processing, like the encoding of neutral verbal material (Erk et al., 2003). Liberzon et al. (2003) together with other researchers (Davis and Whalen, 2001; Whalen et al., 1998, 2001) proposed a general interpretation of the function of the SLEA as a region responding to salient, but somewhat unclear stimuli while the ventral amygdala was interpreted as a region involved in the detection and processing of negatively valenced biologically relevant information. Salient stimuli were defined as stimuli that elicit processing because they are important for biological drives and psychological needs (Liberzon et al., 2003). Therefore, increased SLEA responses upon expecting aversive pictures in depressed patients as found in our study could represent a higher than usual assignment of salience to stimuli announcing negative, uncertain prospects. The information processing bias, as postulated by cognitive theories, may comprise a misassignment of salience and therefore the SLEA is a brain region potentially modulated by this bias also from a neuroanatomical point of view. Moreover, a meta-analysis of Wager et al. (2003)

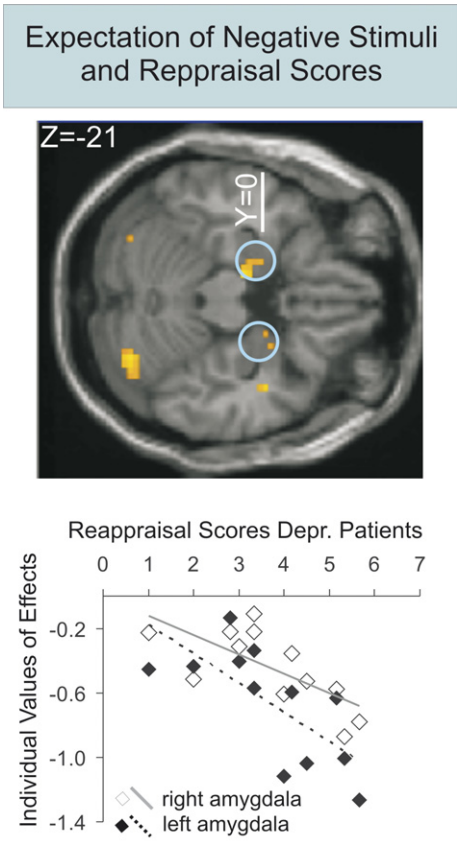

Fig. 5. *Expectation of negative stimuli:* Individual values of modeled effects over the whole brain correlating with individual scores of reappraisal as measured with the Emotion Regulation Questionnaire, ERQ in depressive patients. Correlations were computed with the first level contrast images for the regressor 'Expectation of Negative Stimuli'. *Plots:* Correlation curves (patients) of values of modeled effects at local maxima within left ($r = 0.71$) and right ($r = 0.70$) amygdala and reappraisal scores. Maps were thresholded at $p < 0.006$ uncorrected for multiple comparisons. At this level, we found a correlation between the fMRI signal in the amygdala and reappraisal scores in the patients as depicted.

of findings from neuroimaging concerning functional brain anatomy in emotion points out the important role of SLEA in emotional processing.

Dorsal parts of the amygdala including the SLEA have been associated with modulating vigilance and attention in the presence of stimuli that have gained salience in the past but are currently unclear (Holland et al., 2000). They have been associated with the perception of fearful faces as well (Whalen et al., 2001). Expectation of an unknown picture with salient (negative) valence as in our study may well involve such processes especially in the patients including some own feelings of fear that may evoke similar brain activations as seeing fearful faces. These effects were, on average, observed in all patients. On the contrary, the correlations with Hamilton and Reappraisal scores were found for clearly ventral portions of the amygdala and with strongest activation in the most depressed subjects. Previous studies that found correlations of amygdala activation and scores of negative affect and depression (Abercrombie et al., 1998; Drevets et al., 1992) were resting state PET scans that hardly allowed an exact distinction between ventral and dorsal parts of the amygdala and were not related to a task. However, their findings have been interpreted as indicative for the role of the amygdala as a processor of biologically relevant information (Whalen et al., 2002). The activation could reflect the assignment of relevance to usually not relevant information primarily in the more depressed subjects when expecting a negative picture.

4.3. Perception of anticipated emotional stimuli

Upon presentation of emotional stimuli we found two regions within the cingulate cortex showing elevated activation in patients with depression. Perception of anticipated negative stimuli was associated with increased activation in the dorsal part of the anterior cingulate. Prior studies of depression have pointed out the relevance of anterior cingulate cortex activity within the course of disease. Increased activation of more dorsal parts of the anterior cingulate cortex, as found in our study, have been associated with treatment response or state of remission comparing patients prior to and after treatment (Davidson et al., 2003; Goldapple et al., 2004). Although found compared to healthy controls, the activity found in our study can support these prior findings and may reflect that we measured patients in a state of partial remission.

Presentation of anticipated positive stimuli was associated with a clearly ventral activation of the ACC namely, its subgenual part. Activation of the subgenual part of the ACC has been consistently shown to be related to response to antidepressant treatment (Fu et al., 2004; Mayberg et al., 1997, 2000) with initially enhanced activity attenuating after successful treatment. At the time of the investigation our patients were partially remitted and only moderately depressed. In the context of enhanced activity upon presentation of positive compared to neutral visual stimuli the activation was unexpected and hard to interpret. As the region is very prone to artefacts we tried to rule them out, but our search for artefacts did not deliver results. Further interpretation of the function of this region in depression is pending.

4.4. Emotion regulation strategies

In the original publication of the ERQ that we used to assess emotion regulation in our study, Gross and John (2003) define two major, contrarious emotion regulation strategies: suppression and reappraisal of emotions. In their investigations they showed that reappraisal could help to effectively diminish negative and also enhance positive emotions while suppression as a strategy leads to a reduction in emotion expression but not in actual experience. Reappraisal therefore is regarded as the superior of the two strategies (Gross, 2002).

Our own behavioral data on emotion regulation strategies revealed significantly elevated suppression scores in

depressed patients compared to healthy controls. Suppression scores as measured with the ERQ have been associated with scores of depressive symptoms recently (Gross and John, 2003) showing positive correlations between the two. The fact that our patients with depression used preferentially suppression as an emotion regulation strategy compared to the control group may contribute to the between groups differences in brain activation upon anticipation of emotional stimuli. However, we did not find significant correlations between brain activity and suppression scores. Furthermore, we found reappraisal scores to be negatively correlated with depression ratings. This suggests that the patients with less severe symptoms or upon further recovery preferably applied the supposedly more effective regulation strategy. Correspondingly, we demonstrate a marginal negative correlation of reappraisal scores and bilateral ventral amygdala activation. These results are in line with the findings of Ochsner et al. (2004) who showed that an effective down-regulation strategy with reappraisal reduces amygdalar activity when confronted with negative stimuli.

4.5. Limitations

4.5.1. Depression and anxiety

Depression and anxiety are two diagnostic entities often hard to separate. To put an emphasis on depression in comparison to classical anxiety disorder we used clearly negatively valenced pictures from the IAPS of disgusting but assumably not fear-inducing content. We considered this an appropriate means to investigate the expectation of negative stimuli in depression without primarily measuring fear. Additionally, the fact that amygdalar activity upon expectation of negative stimuli correlated with severity of depression but not anxiety scores further suggests a closer link to depressive symptoms. For a better differentiation, our results should be compared to data of patients with anxiety disorder.

4.5.2. Antidepressive treatment

In our study all patients received stable antidepressant medication of mainly SSRIs. From prior studies of the effects of antidepressant medication, including SSRIs like fluoxetine, it is known that amygdalar activation that is commonly elevated in acute depression attenuates with antidepressive treatment (Fu et al., 2004; Sheline et al., 2001). Therefore, it can be assumed that the hyperactivation of the SLEA/dorsal amygdala as found in our study upon expectation of negative stimuli was rather found *despite* antidepressant medication. Investigating patients in a state of partial remission like we did offers the opportunity to identify persisting factors beyond acute states of the illness (Liotti et al., 2002).

5. Conclusion

Starting from the idea that negative attitudes towards the future according to cognitive theories are an important characteristic of depression we investigated the neural signature of anticipation in patients with unipolar depression and healthy subjects. We found enhanced activation in the dorsal amygdala/SLEA as a potential consequence of altered anticipation processes in patients suffering from depression upon anticipation of negative compared to neutral or positive stimuli. Ventral amygdala activation correlated positively with severity of depression and negatively with reappraisal scores. Supporting cognitive theories, we interpret this finding as evidence from neuroimaging that in depression not only altered emotional perception but as well altered attitudes as involved in expectation result in differences in brain activity particularly in the limbic system.

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